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JOYCE VON NATZMER
PEQUIGNOT + MYERS LLC
200 Madison Avenue
Suite 1901
New York, NY 10016

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/868,967	WALLUKAT ET AL.	
	Examiner	Art Unit	
	JON M. LOCKARD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 12-26* is/are pending in the application.

4a) Of the above claim(s) *1-5 and 12-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-5 and 12-26* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/7/06, 9/20/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group III, corresponding to original claims 6-11 and newly added claims 20-26, in the reply filed on 10 November 2008 is acknowledged. Applicant's election of SEQ ID NO:1 as the species of peptide in the reply filed on 10 November 2008 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-5 and 12-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10 November 2008.

Status of Application, Amendments, and/or Claims

3. The Response filed on 10 November 2008 has been entered in full. Claims 1-3, 5, and 19 have been amended, claims 6-11 have been cancelled, and claims 20-26 have been added. Newly added claims 20-26 will be examined as they fit under the rubric of the elected invention. Claims 1-5 and 12-19 have been withdrawn from further consideration as discussed supra. Therefore, claims 1-5 and 12-26 are currently pending, and claims 20-26 are the subject of this Office Action. The claims also read on the elected species of SEQ ID NO:1, and have been searched to the extent that they read on the elected species.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on 07 April 2006 and 20 September 2007 have been considered by the Examiner.

Specification

5. The disclosure is objected to because of the following informalities:

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Appropriate correction is suggested.

7. The abstract of the disclosure is objected to because it is more than one paragraph in length. Correction is required. See MPEP § 608.01(b).

Claim Objections

8. Claim 20 is objected to because of the following informalities: "A_1" should read "AT_1". Appropriate correction is suggested.

Claim Rejections - 35 USC § 112, 2nd Paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 20-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for

reciting the phrase "contacting said peptides with a body fluid". Without knowing whether the limitation refers to a body fluid from a patient suspected of having preeclampsia, of if it refers to any body fluid from any subject, the metes and bounds of the claims cannot be determined.

12. Claim 20 is rejected as being indefinite for reciting the phrase "binding said auto-antibodies in said body fluid via said peptides". Since the limitation does not set forth any method steps, it is unclear what additional method steps are intended to be encompassed by the claim. Is an additional step intended, or does it refer to the previous step to be carried out under conditions permitting binding of the auto-antibodies to said peptides? Without knowing which is intended, the metes and bounds of the claims cannot be determined.

13. Claims 21-26 are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 112, 1st Paragraph (Scope of Enablement)

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 20-26 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method for (1) detecting autoantibodies against the angiotensin AT_1 receptor in a body fluid comprising contacting an isolated peptide of the AT_1 receptor with a body fluid under conditions permitting binding of said autoantibodies with said peptide, wherein the peptide consists essentially of the amino acid sequence of SEQ ID NO:1, and wherein the body fluid is maternal blood; or (2) binding autoantibodies against the

angiotensin AT_1 receptor in a body fluid *in vitro*, comprising contacting an isolated peptide of the AT_1 receptor with a body fluid under conditions permitting binding of said autoantibodies with said peptide, wherein the peptide consists essentially of the amino acid sequence of SEQ ID NO:1, and wherein the body fluid is maternal blood, does not reasonably provide enablement for binding or detecting autoantibodies, comprising contacting an isolated peptide of the AT_1 receptor with a body fluid and bonding said autoantibodies in said body fluid via said peptide, (2) wherein the peptide comprises 5 to 30 amino acids of the AT_1 receptor or comprises the amino acid sequence of SEQ ID NO:1, (3) wherein the peptide is contacted with the body fluid *in vivo*, or (4) wherein the body fluid is something other than maternal blood. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

16. The specification's disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

17. The claims are drawn very broadly to a method for binding or detecting autoantibodies, comprising contacting an isolated peptide of the AT_1 receptor comprising 5 to 30 amino acids,

wherein said peptides bind autoantibodies occurring in patients with preeclampsia and malign hypertension, with a body fluid, and bonding said autoantibodies in said body fluid via said peptide. The claims also recite wherein the peptide comprises the amino acid sequence of SEQ ID NO:1. While the Specification teaches that the peptide consisting of SEQ ID NO:1 is able to bind and inhibit the effect of autoantibodies against the angiotensin AT_1 receptor (See pg 7, Figure 2), it does not teach a commensurate number of peptides that are encompassed by the scope of the claims that also exhibit these activities. For example, while the Specification teaches that the peptide consisting of SEQ ID NO:1 is able to bind and inhibit the effect of autoantibodies against the angiotensin AT_1 receptor (See pg 7, Figure 2), the Specification also teaches that the agonistic effect of the autoantibodies achieved via the AT_1 receptor was only neutralized by the peptide consisting of the amino acid sequence of SEQ ID NO:1 (See pg 8). Furthermore, the Specification also teaches that SEQ ID NO:1 (an epitope on the second extracellular loop of the AT_1 receptor, has a special importance in preeclampsia, since it was identified an all of the patients examined (See pg 8). Therefore, one skilled in the art would not expect any peptide comprising 5 to 30 amino acids of the AT_1 receptor would be able to bind the autoantibodies of the AT_1 receptor that occur in patients with preeclampsia or malign hypertension.

18. The state of the art is such that the relationship between the sequence of a protein and its activity is not well understood and unpredictable, and that certain positions in the sequence are critical to the protein's structure/function relationship and can only tolerate only relatively conservative substitutions or no substitutions. The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain

functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions and still retain the activity of the peptide having the amino acid sequence of SEQ ID NO:1. Even though the binding site was identified in the specification (the epitope consisting of SEQ ID NO:1), that may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues or the addition of residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2).

19. Due to the large quantity of experimentation necessary to generate the infinite number of variants and derivatives recited in the claims and possibly screen same for activity, the lack of

direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

20. The claims also recite "contacting said peptide with a body fluid", which the Examiner has interpreted as reading on both *in vitro* and *in vivo* methods. The specification teaches that the peptide consisting of SEQ ID NO:1 is able to bind and inhibit the effect of autoantibodies against the angiotensin AT_1 receptor, obtained from the γ-globulin fraction of the serum of preeclampsia patients (See pg 7), in a culture comprising cardiomyocytes (See pg 8). While the Specification provides adequate direction and guidance on how to bind or detect autoantibodies against the AT_1 receptor in a body fluid, i.e., maternal blood, *in vitro*, there is no guidance on how to bind said autoantibodies in the body fluid *in vivo*. One skilled in the art would not know, with any level of predictability, that the administration of an undetermined amount of the peptide of SEQ ID NO:1 would be able to bind autoantibodies of the AT_1 receptor *in vivo*.

21. The specification fails to disclose how to assess *in vivo* a pharmaceutically effective amount of the peptide of SEQ ID NO:1 for binding of autoantibodies of the AT_1 receptor *in vivo*. The art teaches that the goal of delivering proteins and peptides noninvasively has only achieved modest success, with poor applicability to proteins and peptides (See for example Pettit et al.

"The development of site-specific drug-delivery systems for protein and peptide biopharmaceuticals". Trends Biotechnol. 16: 343-349, 1998; See especially pg 343, col 1-2). The problems posed by proteins and peptides are their large molecular size, electrical charge, relatively hydrophilic nature, and relative instability in environments of extreme pH or proteolytic activity (such as the stomach and intestine) (pg 343, col 2). Pettit et al. review several routes of protein administration and the limitations that have been encountered. For example, limited success has been achieved delivering proteins and peptides orally because of: 1) poor intrinsic permeability across intestinal epithelium, 2) susceptibility to enzymatic attack, 3) rapid post-absorptive clearance, and 4) chemical instability (pg 344-345). Although much effort has been given to the transdermal delivery of pharmaceutical products, clinical applications have been limited to non-protein drugs because of the skin's poor permeability to proteins and peptides (pg 343, col 2). Additionally, proteins or peptides administered systemically must resist clearance via molecular filtration by the kidney and clearance by the reticuloendothelial system (pg 345, col 2). Therefore, the state of the prior art establishes the unpredictability of delivering proteins to a subject. In the absence of this guidance, a practitioner would have to resort to a substantial amount of undue experimentation involving the variation in the amount and duration of administration of the peptide of SEQ ID NO:1, and making a determination of whether a successful result was achieved. The instant situation is directly analogous to that which was addressed in *In re Colianni*, 195 USPQ 150, (CCPA 1977), which held that:

> "a "[d]isclosure that calls for application of "sufficient" ultrasonic energy to practice claimed method of fusing bones but does not disclose what "sufficient" dosage of ultrasonic energy might be or how those skilled in the art might select appropriate intensity, frequency, and duration, and contains no specific examples

or embodiment by way of illustration of how claimed method is to be practiced does not meet requirements of 35 U.S.C. 112 first paragraph".

22. There are no working example presented in the instant specification that describe the binding of autoantibodies in vivo utilizing peptides of the AT_1 receptor, and thus does not disclose methods of binding autoantibodies commensurate in scope with the claims.

23. Thus, in view of the lack of teachings and unpredictability of the art set forth above and the lack of working examples, the instant specification is not found to be enabling for a method for binding autoantibodies *in vivo*. It would require undue experimentation and making a substantial inventive contribution for the skilled artisan to discover how to use the Applicants' invention as currently claimed.

Claim Rejections - 35 USC § 112, 1st Paragraph (Written Description)

24. Claims 20, 21, and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

25. The claims are drawn quite broadly to a method for binding or detecting autoantibodies, comprising contacting an isolated peptide of the AT_1 receptor comprising 5 to 30 amino acids, wherein said peptides bind autoantibodies occurring in patients with preeclampsia and malign hypertension, with a body fluid and bonding said autoantibodies in said body fluid via said

peptide. The claims also recite wherein the peptide comprises the amino acid sequence of SEQ ID NO:1. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claims is a partial structure in the form of the recitation comprising 5 to 30 amino acid of the AT_1 receptor or comprising the amino acid sequence SEQ ID NO:1, and a desired functional property in the form of the recitation of "bind autoantibodies occurring in patients with preeclampsia and malign hypertension". However, there is no identification of any particular portion of the structure that must be conserved. While the specification provides adequate written description for a polypeptide consisting of the amino acid sequence SEQ ID NO:1 that bind and inhibit the effect of autoantibodies against the angiotensin AT_1 receptor (See pg 7, Figure 2), it does not provide adequate written description for a commensurate number of the claimed species of peptides that also bind and inhibit the effect of autoantibodies against the AT_1 receptor.

26. As set forth in the Enablement rejection *supra*, the state of the art is such that the relationship between the sequence of a protein and its activity is not well understood and unpredictable, and that certain positions in the sequence are critical to the protein's structure/function relationship and can only tolerate only relatively conservative substitutions or no substitutions. In the instant case, the distinguishing characteristics of the claimed genus are not described. The only adequately described species is the polypeptide consisting of the amino

acid sequence SEQ ID NO:1, and the description of one species of polypeptide (SEQ ID NO:1) is not adequate written description of an entire genus of functionally equivalent polypeptides, which incorporate all variants and derivatives encompassed by the claims.

27. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

28. With the exception of the peptide consisting essentially of the amino acid sequence of SEQ ID NO:1 referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed antagonists, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The product itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

29. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

30. Therefore, only the peptide consisting essentially of the amino acid sequence of SEQ ID NO:1, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Summary

31. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Manjunath N. Rao, Ph.D.**, can be reached on **(571) 272-0939**. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jon M. Lockard, Ph.D.
January 30, 2009

/Jon M Lockard/
Examiner, Art Unit 1647